Sleep Disorders

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Implications for the Elderly, Epidemiology

Sleeping problems constitute one of the most frequently voiced complaints in the elderly. Patients commonly complain about insomnia (i.e., the problem of either falling asleep or sleeping through the night). While increased need for sleep and abnormal daytime sleepiness are frequent phenomena in older people, patients themselves rarely consider this a relevant problem. The present chapter focuses on insomnia, the most important and frequent sleep disorder in the elderly.

Epidemiological studies on the prevalence of insomnia have yielded differing results depending on study method, patient population, and the definition of insomnia (Ancoli-Israel and Cooke 2005). Overall, 30–60% of older people across industrialized nations report suffering from insomnia. Somatic and psychiatric comorbidity, frailty, low income, poor education, and loss of partner are predisposing factors (Bloom et al. 2009; Foley et al. 1999).

Among the elderly, 30–60% of all persons complain about insomnia.

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The prevalence of insomnia is particularly high during inpatient hospital care. Hospitalized patients frequently receive hypnotics: On general wards, 31–41% of all patients are given hypnotics; on surgical wards, the percentage is at 33–88% (Flaherty 2008). These numbers alone point to the significance of insomnia.

In everyday practice, sleep disorders in elderly patients are either frequently not treated at all or, even more often, not adequately treated. Among the most frequent treatment mistakes are

- Long-term prescription of hypnotics
- Lack of careful assessment of patients' medical history
- Failure to properly diagnose patients' complaints.

Often, all three mistakes are committed in combination.

One reason for the lack of attention with regard to sleep disorders is the false belief that sleep disorders constitute only minor health problems. In fact, however, sleep disorders represent a complex, multifactorial geriatric syndrome (Vaz Fragoso and Gill 2007) with numerous causes that has considerable effects on the quality of life of patients as well as consequences on somatic disorders (Wolkove et al. 2007). Patients suffering from sleep disorders have a higher risk for developing high blood pressure and depression as well as cardiovascular and cerebrovascular disorders. Vice versa, these disorders predispose patients for developing sleep disorders. In addition, sleep disorders represent an important cause for reduced cognitive function.

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For example, patients suffering from sleep apnea will often visit their physician because of cognitive deficits instead of sleep problems.

The majority of elderly patients with insomnia are not treated adequately. Indiscriminate prescription of hypnotics is a frequent treatment mistake.

With increasing age, changes in physiological sleep structure and need for sleep may occur (Bloom et al. 2009; Vaz Fragoso and Gill 2007). While infants require 16–20 h of sleep per day, the amount of sleep required by adults amounts to only 7–8 h, that of older persons over 60 years of age to only 6.5 h. Of course, these are only average values; a person's individual need for sleep varies greatly. In addition to a shorter overall sleep duration, the proportion of deep delta-sleep cycles (stages III and IV) and REM (rapid eye movement) sleep is also reduced. Furthermore, sleep-wake-cycles also undergo changes, with older people going to bed and waking up earlier than younger adults. In the elderly, sleep is highly fragmented, which is in part due to a lower arousal threshold to external stimuli.

These physiological changes in association with advanced age explain a large portion of subjective sleep disorders in the elderly. Many patients already profit from the mere information that their subjectively perceived sleep deficit is not a sign of illness, but rather the result of naturally occurring changes in the amount of sleep needed in older age.

In the elderly, sleep disorders may be triggered by a whole host of possible causes. Within this context, it is sensible to differentiate between primary, idiopathic sleep disorders and comorbid (secondary) sleep disorders as a complication of other illnesses or as a side effect of medication. The exact cause-effect relationship, however, remains often unclear in patients with comorbidities associated with sleep disorders. The following summary as well as Table 1 show the most frequent causes of primary and comorbid sleep disorders.

Comorbidities and medication often contribute to sleep disorders in the elderly.

Overview of Frequent Sleep Disorders in the Elderly

1. Primary specific sleep disorders
   - Circadian sleep disorders
   - Sleep apnea syndrome
   - Restless legs syndrome
   - REM sleep disorders
   - Periodic leg movements during sleep.
2. Comorbidities associated with sleep disorders
   - 2.1. Somatic disorders
     - Pain syndromes
     - Heart disease, nocturnal angina pectoris
     - Obstructive lung disease, chronic rhinitis
     - Reflux disorder, diarrhea, obstipation
     - Nocturia, incontinence.
   - 2.2. Neurological-psychiatric disorders
     - Stroke
     - Parkinson's disease
     - Dementia
     - Delirious states
     - Major depression.
   - 2.3. Behavioral aspects
     - Inactive lifestyle
     - Afternoon nap
     - Early bedtime
     - Alcohol, coffee, black tea during evening hours
     - Heavy meals during evening hours.
   - 2.4. Environmental factors
     - Noise, light, unfavorable room temperature
     - Unsuitable bed or bed linens.

Therapeutically Relevant Special Features of Elderly Patients

Adequate treatment of insomnia in the elderly should include the following therapy goals:

1. Careful clarification of all causes requiring treatment,
2. Thorough patient information,
3. Improvement of sleep disturbances and, as a consequence,

Table 1 Medication and other compounds frequently associated with sleep disorders (selection)

Substance	Remark
Alcohol	Induces sleep, but shortens and fragments sleep duration
Caffeine, black tea	Should not be consumed during evening hours
Nicotine	Stimulating effect
Amphetamine	Stimulating effect, sleep disturbances, nightmares
Antidepressants (SSRI/SSNRI, bupropion)	Sleeplessness as frequent side effect
Tricyclic antidepressants, mirtazapine	Increased sleepiness
Thyroxine	Overdosing leads to sleeplessness, underdosing may cause hypersomnia
Theophylline	Increases sleeplessness
Phenytoin	May cause sleeplessness or sleepiness
Diuretics	Increased nocturia, medication should preferably be taken in the morning
Levodopa and other dopaminergic Parkinson medications	Insomnia, nightmares
Beta-blockers	Change in sleep architecture
Acetylcholine esterase inhibitors, memantine	Insomnia, nightmares
Glucocorticoids	Stimulating effect, insomnia, nightmares

SSRI selective serotonin reuptake inhibitor, *SSNRI* selective serotonin norepinephrine reuptake inhibitor.

4. Improvement of patients' quality of life and general health.

As a rule, the diagnostic and therapeutic principles do not differ from those in younger adults.

The following overview summarizes the relevant diagnostic and therapeutic procedures.

Treating Elderly Patients Suffering from Insomnia

- Sleep history
  - Determine whether patient is actually suffering from insomnia
  - Precise history of symptoms (sleep onset, duration, and course)
  - 24-h sleep pattern (wake/sleep cycles)
  - Family history of sleep disorders (e.g., sleep apnea)
  - Sleep history by significant other/sleeping partner.
- Examinations
  - Sleep diary (at least over 1 week)
  - Physical and psychiatric examination
  - Laboratory tests and technical examinations according to individual conditions.
- Diagnosis
  - Primary sleep disorder
  - Comorbid sleep disorder
    - Somatic disorders
    - Psychiatric disorders
    - Behavior-related sleep disorders
    - Sleep disorders caused by external factors
    - Medication effects.
- Treatment
  - Treatment of primary causes whenever possible
  - Informing patients about their disorder
  - Measures of sleep hygiene
  - Nonpharmacological measures
  - Pharmacological treatment if absolutely necessary
  - When appropriate, referral to specialist.

In light of the extensive range of differential diagnoses, it goes without saying that the assessment and treatment of sleep disorders in the elderly is complex. A brief consultation at the general practitioner's office does not suffice when an extensive medical history and careful differential diagnosis are called for. Whenever family practitioners cannot afford to invest the time necessary for performing these steps, it is undoubtedly advisable to send older patients with insomnia to a specialist or specialized medical center instead of starting inadequate

pharmacological treatment without prior careful screening due to a lack of time.

By far the most frequent mistake in the treatment of insomnia in elderly patients is the common practice to prescribe hypnotics without adequate diagnostic evaluation.

Initially, it is of particular importance to determine whether patients are indeed suffering from a sleep disorder in need of medical treatment. Many older people complain about sleeplessness; often, however, a careful analysis of sleep patterns and sleep durations reveals that these patients actually have normal sleep duration, but that their daily life offers so few activities and distractions that they subjectively perceive their sleep duration as being too short. In this large patient population, pharmacological interventions would be contraindicated. In case of comorbid sleep disorders, physicians must first attempt to treat the potentially underlying cause before additional symptomatic treatment is indicated. A summary of the most important differential diagnoses is provided in the overview on frequent causes of sleep disorders in the elderly. As case in point, the symptomatic treatment of sleep apnea syndrome with sedating hypnotic medication would in fact contribute to the deterioration of symptoms, whereas adequate treatment not only would improve the symptom of insomnia but also would alleviate a major cardiovascular risk factor.

In numerous patients, an extensive analysis of sleep and behavior patterns will reveal factors that could be directly implemented in a discussion of sleep hygiene (see summary).

Measures for Improving Sleep hygiene in Patients with Insomnia

- Beds should only be used for sleeping and sexual activities
  Patients should leave the bed whenever they cannot fall asleep and engage in other activities before returning to bed.
- No daytime naps
  Patients should not sleep or lay down to rest during the day; at night, they should refrain from going to bed too early.
- Ensure an optimal sleep environment
  Low noise level, optimal and comfortable temperatures, ventilation, light sources, and bed linens, and so on should be taken into consideration.
- Avoiding activities that have a deleterious effect on sleep
  Patients should refrain from consuming alcohol, heavy meals, nicotine, or coffee during evening hours.
- Activities to promote sound sleep
  During the day, patients should be physically active and plan different measures and sleep rituals, such as a warm bath, relaxation exercises, yoga, sleep-promoting teas, or small meals rich in tryptophan (e.g., bananas) or carbohydrates.

When taking older patients' history, it often becomes apparent that many patients complaining of insomnia tend to spend their days rather inactively, maybe even lay in bed during the day, take a nap in the afternoon, or go to bed very early in the evening. Under these circumstances, it is not surprising that the duration of their nighttime sleep cannot be long. Simply by modifying these behavior patterns, patients can achieve improvement of their symptoms.

Before prescribing medication, physicians should first exhaust all nonpharmacological measures available, such as, for example, all measures and techniques for improving sleep hygiene. In some patients, specific measures such as behavior therapy or light therapy may be of use. For many patients with sleep disorders, learning relaxation techniques such as autogenic training, progressive muscle relaxation, or yoga proves to be helpful.

Improving sleep hygiene and other nonpharmacological approaches have priority over pharmacological interventions.

With regard to the pharmacological treatment of insomnia, we differentiate between acute or chronic insomnia. Typical examples for acute insomnia are grief and bereavement or inpatient hospital treatment, when unfamiliar environment and external disturbing factors such as nightly rounds or snoring roommates constitute disturbing factors. In these patients, temporary

pharmacotherapy with hypnotics may indeed be useful. Generally, however, medication with hypnotics should not exceed a period of about 10 days.

With acute insomnia in association with temporarily stressful situations, the use of a hypnotic substance for a maximum of 10 days may be indicated.

Generally not useful, on the other hand, is the prescription of hypnotics in patients with chronic insomnia. Instead, physicians are called on to ward off the frequently voiced wish of patients for medication and to suggest alternative, nonpharmacological treatment approaches. Given for chronic insomnia, pharmacological substances have numerous disadvantages: Due to their centrally active sedative effect and muscle relaxant properties, benzodiazepines, and to some degree also nonbenzodiazepine hypnotic agents, reduce muscle tone and increase patients' risk of falling (see chapter "Fall Risk and Pharmacotherapy"). Many substances, particularly benzodiazepines and nonbenzodiazepine benzodiazepine receptor agonists ("Z-drugs," e.g., zolpidem), are associated with a high addiction risk, particularly if taken over longer stretches of time. Other medication groups such as antidepressants or antipsychotic drugs that are frequently employed as hypnotics are associated with a considerable potential for side effects, while the long-term efficacy and safety of newer substances, such as extended-release melatonin or melatonin receptor agonists, have not been sufficiently examined in older patients.

In patients with chronic insomnia, pharmacological interventions should generally be avoided.

Under ideal circumstances, in which both physicians and patients act in accordance with state-of-the-art medical knowledge, hypnotics would rarely be used to treat chronic insomnia. In reality, however, hypnotics are among the most frequently prescribed medication groups despite numerous side effects and an overall low efficacy profile in older patients. This is mainly for the sake of physicians' convenience, for whom handing out prescriptions is easier than getting involved in lengthy and often poorly paid consultations on sleep hygiene and behavior. Moreover, although many patients experience high psychological strain in association with their sleep disorder, unfortunately they are often not motivated or able actually to implement even simple useful rules on sleep hygiene or behavioral modifications.

It is thus not surprising that hypnotics represent the substance group that is most frequently abused by older patients. Unfortunately, neither the general public nor physicians show particular sensibility with regard to medication abuse in the elderly, so that the great majority of addiction disorders involving legal substances are not diagnosed and remain untreated. In the United States, approximately 11% of elderly citizens are thought to abuse medication, with hypnotics prescribed for the treatment of insomnia playing the most important role (Culberson and Ziska 2008). According to a large-scale study, in 2001, nearly a quarter of all patients in nursing homes were unnecessarily treated with benzodiazepines (Svarstad and Mount 2001).

Unfortunately, many physicians have been swayed by misleading marketing strategies to consider nonbenzodiazepine benzodiazepine receptor agonists to be unproblematic or "safe" concerning the development of addiction. This is a major reason why nonbenzodiazepine benzodiazepine receptor agonists are incorrectly prescribed over longer stretches of time and have replaced benzodiazepines as a hypnotic of first choice. In many countries, there is some uncertainty on the prescription of benzodiazepines as benzodiazepines like nonbenzodiazepine benzodiazepine receptor agonists are inexpensive and increasingly prescribed by way of private prescription or obtained via the Internet, thus escaping statistical recording. It has to be emphasized that in the development of medication addiction in elderly patients, in contrast to addiction disorders in young patients, physicians play the most important role. Accordingly, the prescription of these substances should be handled exceedingly restrictively, prescribing only minimal quantities and only if clearly indicated. However, many patients manage to acquire

their addictive drug through "doctor shopping" by consulting different physicians as a means of securing repeat prescriptions for their drug of choice or by buying their drugs over the Internet.

Medication abuse is a frequent problem among the elderly. Due to uncritical and incorrect prescription practices, hypnotics are the most frequently used drugs of abuse.

Evidence-Based, Rationalistic Drug Therapy and Classification of Drugs According to Their Fitness for the Aged (FORTA)

Reflecting the insufficient data from adequate clinical trials on hypnotics in the elderly, there is a substantial heterogeneity between different countries or continents in the selection and use of these medications. Drugs that are commonly prescribed in some countries may not be available at all in other regions. For example, eszopiclone, one of the most commonly employed hypnotic agents in the United States, is not licensed in Europe. Trazodone, another substance frequently used in the United States to treat insomnia, is only rarely prescribed in Europe. On the other hand, in many European countries there is a tradition of off-label use of low-potency typical antipsychotics such as pipamperone or melperone to promote sleep in elderly patients, which is not a frequent practice in other countries. Scientific evidence is almost nonexistent for both trazodone and low-potency typical antipsychotics to treat insomnia in elderly patients.

Suitability of Substance Groups for Use in the Elderly

As a rule, the use of hypnotics should be avoided with sleep disorders. If at all, they should only be used in acute sleep disorders over a short treatment period. A summary of frequently prescribed hypnotics is found in Table 2.

An example for a pragmatic incremental regimen for short-term treatment with hypnotics in inpatients is shown in the overview that follows. The information provided relates only to the short-term application of hypnotics over a maximum period of 10 days in hospitalized patients. Beyond this time frame, the use of hypnotics is generally not recommended in elderly patients, although some of these substances have been licensed for use without time limitations. Whenever hypnotics must be administered for longer periods due to individual considerations (e.g., in dementia disorders, in palliative medicine, with major depression, etc.), the indication should be reassessed regularly, and a concept for possible dose reductions should be established.

Escalation Scheme for Short-Term Pharmacological Treatment of Insomnia in Elderly Patients (Example)

This scheme was developed for older patients undergoing inpatient treatment. The respective contraindications for each drug must be considered on an individual basis. As a rule, the duration of treatment should not exceed 10 days. The listing of the drugs is based on clinical experience and not on a purely scientific basis. Extended-release melatonin is not approved by the Food and Drug Administration (FDA), but freely available as a supplement in the United States. Alternatively, ramelteon may be used (8 mg).

General Rules

- Sleeping pills should be avoided.
- For the treatment of sleep disorders, benzodiazepines should only be used under particular circumstances.
- Sleep medication should generally not be administered after midnight (for exceptions, see the following discussion).

First Step: Eszopiclone

- Give an initial dose of 1 mg eszopiclone before bedtime.
- Given lack of effect, an additional dose of 1 mg should be administered after 30 min.
- Patients who had previously been given 2 mg should possibly be started on that dose.

Table 2 Pharmacological compounds frequently used for the treatment of insomnia in elderly patients

Drug	Compound group	Dosage in older patients	FORTA	Remarks
Zolpidem	Nonbenzodiazepine benzodiazepine receptor agonist	5–10 mg	C	For short-term treatment (<10 days) of acute insomnia after nonpharmacological measures have failed and treatment is absolutely necessary. Low efficacy. Risk for addiction with longer use
Zopiclone	GABA receptor agonist	3.75–7.5 mg	C	See zolpidem
Eszopiclone	GABA receptor agonist	0.5–2.0 mg	C	See zolpidem. S-enantiomer of zopiclone. Studies on prolonged use are available. However, in elderly patients, prolonged use is not recommended
Zaleplone	Nonbenzodiazepine benzodiazepine receptor agonist	5–10 mg	C	See zolpidem. Due to its short half-life particularly useful with sleep-onset disorders
Oxazepam	Benzodiazepine	10 mg	D	Poor efficacy, numerous side effects. High risk for addiction. Not recommended
Triazolam	Benzodiazepine	0.25 mg	D	Poor efficacy, numerous side effects. High risk for addiction. Not recommended
Pipamperone	Antipsychotic with sedative effect	Initially 20 mg, increase up to 80 mg/ at night[a]	C	Effect not shown, numerous side effects. Despite lack of scientific proof of efficacy suitable for short-term use with acute sleep disorder based on extensive clinical experience. Drug of second choice
Mirtazapine	Noradrenergic and serotonergic AD	15 mg, possible increase to 30 mg[a]	D[b]	Orthostatic dysregulation. Weight gain. Metabolic effects. Efficacy not shown. Not recommended for use in patients not suffering from depression
Opipramole	Tricyclic anxiolytic	50 mg[a]	D[b]	Efficacy not shown, numerous side effects. Not recommended for use in older patients
Doxepin	Tricyclic antidepressant	25–50 mg[a]	D[b]	Efficacy not shown, numerous side effects. Not recommended
Trazodone	Tricyclic antidepressant	25–100 mg[a]	D[b]	Efficacy not shown, numerous side effects. Not recommended
Diphenhydramine	Antihistamine	50 mg	D	Efficacy not shown, numerous side effects. Not recommended
Ramelteon	Melatonin receptor agonist	8 mg	C	Well tolerated. No risk for developing tolerance or withdrawal symptoms. Low risk for addiction. No extensive experience. Low efficacy. Drug of second choice for short-term treatment of acute insomnia
Melatonin (extended release)	Melatonin	2–4 mg	C	Not FDA approved. Available as a supplement in the United States. Well tolerated. No risk for developing tolerance or withdrawal symptoms. Low risk for addiction. No extensive experience. Most likely low efficacy. Drug of second choice for short-term treatment of acute insomnia

The reference substances listed are frequently used in everyday clinical practice for the treatment of insomnia in older patients. Their superiority over comparable substances not listed in this table has not been shown. FORTA classifications strictly refer to short-term use of no longer than 10 days after nonpharmacological measures have failed and when therapy is absolutely necessary.

AD antidepressant, *FDA* Food and Drug Administration, *FORTA* Fit for the Aged.

[a]Dosage recommendations based on clinical experience.

[b]Listing refers to the indication "insomnia".

- Give a maximum dose of 2 mg eszopiclone at night.
- In countries where zopiclone is available, zopiclone can be employed as an equivalent (starting dose 3.75 mg, maximum dose 7.5 mg/night).

Second Step Given Lack of Efficacy of Step 1: Extended-Release Melatonin (Not FDA Approved, Supplement in the United States)

- Give an initial dose of 2 mg extended-release melatonin.
- Given lack of effect, an additional 2 mg of extended-release melatonin may be given after 30 min.
- Patients who had previously already received the maximum dose may be started on 4 mg extended-release melatonin.
- Give a maximum dose of 4 mg extended-release melatonin per night.

Medication After Midnight

Medication should only be administered after midnight if no other sleep medication has been given during the night. As a rule, sleep medications should never be administered after 3 a.m.

- If sleep medication after midnight is unavoidable:
  - Step 1: Give 2 mg extended-release melatonin.
  - Step 2: Given lack of effect, one additional dose of 2 mg extended-release melatonin may be administered after 30 min.
- Patients who had previously failed to respond to 2 mg extended-release melatonin may immediately receive an initial one-time dose of 4 mg slow-release melatonin.
- In countries in which zaleplon (FDA approved) is available, 5 mg zaleplon can be used as an alternative to extended-release melatonin.

Treatment Approaches in Patients Who Primarily Experience Problems with Falling Asleep (No Disturbance of Sleep Continuity)

- Step 1: Give 2 mg extended-release melatonin (alternatively 5 mg zaleplon, if available).
- Step 2: Given lack of efficacy of Step 1, an additional, one-time, dose of 2 mg extended-release melatonin may be administered after 30 min.
- Given lack of effect after 30 min, proceed as described previously.

Specifically in the elderly both the efficacy and the tolerability of hypnotics have scarcely been examined. There are hardly any valid clinical trials comparing the different substances in elderly individuals.

The compounds cited in this chapter are those frequently administered to older patients in day-to-day practice. This does not imply that substances that have not been discussed within this chapter are inferior to those mentioned.

Benzodiazepines

In 1960, the first benzodiazepine was introduced to the market under the trade name Librium® (chlordiazepoxide), followed by diazepam in 1963. In 1970, flurazepam was approved, the first benzodiazepine specifically sold to treat sleep disorders. Compared with their predecessors (i.e., barbiturates and chloral hydrate), benzodiazepines quickly prevailed due to their greater efficacy and fewer adverse effects. A major advantage was the wide therapeutic spectrum of benzodiazepines, which rapidly led to a marked reduction in suicide rates due to medication overdose that had been alarmingly high in association with barbiturates. The most important problem in association with benzodiazepines (i.e., the rapid development of medication tolerance and dependency) was initially not appropriately recognized.

Today, a large number of benzodiazepines are available, differing not only with regard to their pharmacokinetic properties but also concerning their efficacy on different aspects, such as anxiety, sedation, and sleep promotion.

In young adults, the efficacy of benzodiazepines in the treatment of sleep disorders is well documented. In older patients, their usefulness for the treatment of insomnia is far less convincingly established. A meta-analysis of all available studies of sedative hypnotics (benzodiazepines and nonbenzodiazepine benzodiazepine receptor agonists) in older patients showed a significant improvement with regard to important sleep

parameters, although the absolute effect size was relatively small and of questionable clinical relevance (Glass et al. 2005). The rate of undesired side effects in association with hypnotics, on the other hand, was increased, leading the authors to conclude that this relatively low benefit does not justify the risk.

A number of problems limit the use of benzodiazepines. Many substances and their active metabolites have a very long half-life and long effective duration, which will often lead to a hangover with daytime sleepiness during the following day. In the elderly, the half-life of flurazepam, for example, may exceed 100 h. This problem affects particularly older patients, whose metabolism has slowed considerably due to their advanced age, or patients with liver failure, in whom the effect of a single dose of a benzodiazepine may last for many days. For these reasons, short-acting benzodiazepines such as triazolam, with a half-life of 1.5–5 ho, were developed. Due to an increased risk of abuse and addiction, lorazepam should not be prescribed to treat sleep disorders.

In the elderly, a markedly increased risk for falls due to the centrally active sedating and muscle-relaxing effect of benzodiazepines is well documented (see chapter "Fall Risk and Pharmacotherapy").

Particularly in older patients with prior cognitive impairment, benzodiazepines will lead to the aggravation of cognitive deficits. Accordingly, benzodiazepines should be avoided in patients with dementia or mild cognitive impairment.

The half-life of benzodiazepines may be reduced within a few days, thereby increasing the risk of development of tolerance and addiction. Following prolonged use, patients will almost always develop withdrawal symptoms, which may even be life threatening. These include

- Epileptic seizures
- Autonomous nervous system dysfunction
- Agitation and anxiety
- Delirious states

After prolonged benzodiazepine consumption, withdrawal attempts should only be carried out under close outpatient supervision or, preferably, on an inpatient basis.

Under these considerations, benzodiazepines are not recommended for the treatment of sleep disorders in older patients.

Frequent side effects of benzodiazepines are risk for falls, sedation, and development of addiction. Benzodiazepines are not recommended to treat insomnia in older patients.

Nonbenzodiazepine Benzodiazepine Receptor Agonists

During the 1980s, nonbenzodiazepine benzodiazepine receptor agonists (Z-drugs) were introduced to the market. Although these substances act on the ω1 subunit of the benzodiazepine receptor, their chemical structure is not related to that of benzodiazepines. Due to their mode of action, they are associated with similar effects and side effects as benzodiazepines.

Compared with benzodiazepines, however, these substances have several advantages. They do not lead to the development of tolerance, have an overall shorter effective period, and are thus less frequently associated with daytime sleepiness and sedation the next morning. Due to these advantages nonbenzodiazepine benzodiazepine receptor agonists have replaced benzodiazepines as drugs of first choice to treat insomnia.

While initially the risk of potential abuse in association with nonbenzodiazepine benzodiazepine receptor agonists was falsely considered to be very low, these substances now take second place to benzodiazepines as the most frequent cause of medication abuse in the elderly. With prolonged use of more than 4 weeks, nonbenzodiazepine benzodiazepine receptor agonists may show an addiction potential comparable to that of benzodiazepines (Kupfer and Reynolds 1997). Moreover, their use has been linked to the development of depression (Kripke 2007).

The most commonly used nonbenzodiazepine benzodiazepine receptor agonists is zolpidem. The short-acting substance zaleplone has been taken off the market in many countries. Strictly speaking, zopiclon and eszopiclone (the S-enantiomer of zopiclone is FDA approved but not available on the European market) do not belong to the group of nonbenzodiazepine benzodiazepine receptor agonists as they do not exert their GABAergic effects

via the benzodiazepine site of the GABA receptor complex. However, they are commonly listed in this group of substances, although this is not correct from a pharmacological point of view.

Overall, data on the use of nonbenzodiazepine benzodiazepine receptor agonists in older patients are sparse. Based on their meta-analysis of all research trials in older patients, Dolder et al. (2007) concluded that while only showing a modest effect on sleep quality and sleep onset latency, but not sleep duration, these drugs—unlike benzodiazepines—are generally well tolerated. Most frequently reported side effects were headaches, dizziness, and fatigue, which, however, were seen as frequently under placebo. In general, there was no relevant development of tolerance in association with nonbenzodiazepine benzodiazepine receptor agonists.

In the elderly, nonbenzodiazepine benzodiazepine receptor agonists lead to a modest improvement in sleep quality and sleep onset latency while being generally well tolerated.

In comparison with benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists have a smaller impact on patients' muscle tone and risk of falling. To date, only zolpidem has been clearly associated with an increased risk for falls, although this may be explained by the fact that this substance has been analyzed most extensively. Among the rarer but clinically relevant psychiatric complications in elderly patients are delirium, hallucinations, and delusions.

After discontinuing medication, patients may experience rebound insomnia. Overall, however, withdrawal effects are generally much less pronounced than with benzodiazepines.

To date, potential differences between individual nonbenzodiazepine benzodiazepine receptor agonists have not been examined extensively, so that clear differential recommendations cannot be offered (Dundar et al. 2004).

In most countries, zolpidem is one of the most frequently prescribed nonbenzodiazepine benzodiazepine receptor agonists. With a half-life of 2.5 h, zolpidem does not change sleep architecture or lead to the development of tolerance.

With a half-life of only 1 h, zaleplon has the shortest half-life of all nonbenzodiazepine benzodiazepine receptor agonists. Accordingly, zaleplon is particularly well suited for treating sleep onset delays. However, the substance is not marketed in all countries.

As GABA receptor agonists, zopiclone and eszopiclone have a slightly different mode of action but are commonly nonetheless listed among the group of nonbenzodiazepine benzodiazepine receptor agonists. The half-lives are 5.5 and 6.5 h, respectively. In general, zopiclone and eszopiclone exert only a minimal impact on patients' performance during the following day.

Eszopiclone is the S-enantiomer of the racemate zopiclon. Eszopiclone was introduced to the market shortly before the end of the patent protection of zopiclone. Whether the substance actually shows clinically relevant advantages over zopiclon has not been unequivocally proven (Hair et al. 2008). As a consequence, the European Medicines Agency (EMA) did not consider eszopiclone as a "new active substance," causing the manufacturer to refrain from introducing it to the European markets. Eszopiclone has a half-life of 6.5 h. Results from a meta-analysis of five trials showed good tolerability and efficacy, particularly in elderly patients (Melton et al. 2005). Eszopiclone is one of the very few substances for which studies over a longer period of time have been conducted, demonstrating good efficacy as well as tolerability and no development of tolerance over a period up to 3 months in elderly patients (Ancoli-Israel et al. 2010).

Antidepressants

Antidepressants have not been developed for the treatment of sleep disorders and not approved for this indication. Traditionally, antidepressants with sedative side effects are nevertheless frequently used off label to treat insomnia.

Typically, tricyclic antidepressants such as trazodone, opipramole (not available in the United States), and mirtazapine are given at lower doses than those necessary to treat depression. While opipramole is not an antidepressant but used against anxiety disorders, it is listed here due to its related chemical structure.

To date, we do not have sufficient evidence from clinical studies to support the use of

antidepressants against insomnia. Research on the efficacy of antidepressants in sleep disorders has almost exclusively been conducted in patients with depression, in whom insomnia is often a key symptom.

Neither the effectiveness nor the optimal dose of antidepressants in the treatment of insomnia without accompanying depression have been demonstrated. The limited number of studies in primary insomnia did not yield results supporting the use of antidepressants (Erman 2005).

Aside from the fact that there are almost no data showing their efficacy, the numerous adverse side effects of the individual substances speak against the use of antidepressants in older patients.

In light of unproven efficacy and well-documented side effects, the use of antidepressants for the treatment of insomnia without accompanying depression is not recommended.

Antipsychotics

As is the case with antidepressants, antipsychotics have not been developed for the treatment of sleep disorders. In clinical practice, however, many physicians take advantage of the sedating side effect of most antipsychotics to treat sleep disorders. Particularly older, low-potency typical antipsychotics are given at low doses due to their less-pronounced antipsychotic but pronounced sedative properties.

In parallel to inconclusive clinical studies in antidepressants, there are no large systematic studies supporting the use of antipsychotics in sleep disorders. Their optimal doses for the treatment of sleep disorders are not known. At the same time, antipsychotics have a high rate of side effects, such as

- Extrapyramidal symptoms
- Negative metabolic effects
- Weight increase
- Malignant neuroleptic syndrome in rare cases
- Association with increased mortality in patients with dementia.

Despite the aforementioned lack of scientific evidence, physicians have been using antipsychotics in everyday clinical practice. From European experiences, pipamperone, melperone, and tiapride (not FDA approved) are well tolerated given over a limited number of days. However, this observation is not based on scientific data but rather on clinical experience.

The efficacy and tolerability of antipsychotics in the treatment of insomnia have not been sufficiently assessed.

Melatonin and Melatonin Receptor Agonists

Large randomized studies of chemically unaltered melatonin are not available, likely due to the missing commercial potential of this substance, which is produced naturally in the body and thus difficult to license. Smaller studies could demonstrate advantages with regard to sleep quality and sleep onset latency. From a theoretical viewpoint, melatonin is particularly useful in sleep onset disorders. Given short-term use, the substance is well tolerated. While melatonin is not available in some countries, the substance is freely available as a nutritional supplement in the United States and several other countries. However, nutritional supplements hardly guarantee sufficient pharmacological quality control. As their optimal dose is also unknown, the consumption of such supplement preparations must be discouraged.

Recently, an extended-release preparation of melatonin (extended-release preparations of melatonin are available as a supplement in the United States) has been approved in Europe for the treatment of sleep disorders specifically in persons older than 55 years of age. While the respective approval trials (phase III trials) showed excellent tolerability, its effect was comparably small. As there are relatively few data on the long-term use of melatonin, the substance is only approved for short-term use. The risk for the development of tolerance or addiction is presumably low. Thus far, clinical experience with retarded melatonin suggests good tolerability in older patients. Again, however, its effect is apparently comparably small. In cases of predominant sleep onset disorder, melatonin appears useful.

Recently, the selective melatonin agonist ramelteon, carrying additional effects as a serotonin reuptake inhibitor, has been introduced in the United States and several other countries. While its short-term tolerability is excellent, its effect size was small. Largely for this reason, the substance was not approved for use in Europe. The long-term tolerability has not been well investigated yet.

Antihistamines, Anticonvulsives, Phytotherapeutic Agents, and Chloral Hydrate

The very heterogeneous substances antihistamines, anticonvulsives, phytotherapeutic agents, and chloral hydrate were grouped together as neither their efficacy nor their tolerability in older patients has been sufficiently examined to allow for reliable recommendations.

In patients with pain syndromes and depression, pregabalin has been shown to have a positive influence on sleep quality and sleep duration. Whether this finding also holds for patients with insomnia has not been shown thus far. Occasionally, physicians take advantage of the sedating effect of valproic acid for the treatment of sleep disorders. Based on scientific data, this approach cannot be justified.

Diphenhydramine is a freely available, low-priced, first-generation antihistamine substance frequently used to treat insomnia. Neither its use nor possible side effects have been thoroughly examined. The few available studies on diphenhydramine have either yielded inconclusive results or were methodologically flawed (Ancoli-Israel and Cooke 2005). Its sedative effect is subject to the swift development of tolerance. In addition, diphenhydramine and other antihistamines also show anticholinergic effects rendering its use in elderly patients problematic. As a case in point, the use of diphenhydramine led to pronounced cognitive deficits in older patients who had previously shown no cognitive impairment.

Due to their anticholinergic side effects and uncertain efficacy, diphenhydramine and other antihistamines are not recommended for use in elderly patients.

To this day, the hypnotic chloral hydrate that was first introduced in 1869 is still used occasionally. There are no reliable studies of its efficacy, but a number of well-documented side effects, such as rapid induction of tolerance, prolongation of the QT interval, liver failure, and its addiction potential, speak against its use.

Numerous over-the-counter drugs, such as St. John's wort, camomile, hops, kava kava, and passion flower extracts, are marketed for the treatment of sleep disorders. For none of these substances, however, are there adequate data on efficacy and tolerability. In many countries, the sale of kava extracts is prohibited due to isolated cases of associated liver failure. Finally, the pharmaceutical quality of many of these products is not guaranteed.

Principally, considerable placebo effects can be assumed in the treatment of sleep disorders. Keeping this in mind, physicians should not actively advise against the consumption of harmless phytopharmaceuticals if they are well tolerated and patients experience subjective improvement of symptoms.

Classification of Drugs for the Prevention and Therapy of Sleep Disorders (Insomnia) According to Their Fitness for the Aged (FORTA)

(See Chapter "Critical Extrapolation of Guidelines and Study Results: Risk-Benefit Assessment for Patients with Reduced Life Expectancy and a New Classification of Drugs According to Their Fitness for the Aged")

Substance class	Compound	FORTA classification
Nonbenzodiazepine benzodiazepine receptor agonist	Zolpidem, zaleplone	C
GABA receptor agonist	Zopiclone, eszopiclone	C
Benzodiazepine	Oxazepam, triazolam	D
Antipsychotic with sedative effect	Pipamperone, melperone	C[a]
Noradrenergic and serotonergic AD	Mirtazapine	D[a]
Tricyclic anxiolytic	Opipramole	D[a]

(*continued*)

Tricyclic antidepressant	Doxepin, trazodone	D[a]
Antihistamine	Diphenhydramine	D
Melatonine receptor agonist	Ramelteon	C
Melatonin (extended release)	Melatonin	C[a]

[a]Not approved for the treatment of insomnia in all countries; in everyday practice, however, frequent off-label use.

References

Ancoli-Israel S, Cooke JR (2005) Prevalence and comorbidity of insomnia and effect on functioning in elderly populations. J Am Geriatr Soc 53:S264–S271

Ancoli-Israel S, Krystal AD, McCall MV et al (2010) The effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. Sleep 33:225–234

Bloom HG, Ahmed I, Alessi CA et al (2009) Evidence-based recommendations for the assessment and management of sleep disorders in older persons. J Am Geriatr Soc 57:761–789

Culberson JW, Ziska M (2008) Prescription drug misuse/abuse in the elderly. Geriatrics 63:22–31

Dolder C, Nelson M, McKinsey J (2007) Use of non-benzodiazepine hypnotics in the elderly: are all agents the same? CNS Drugs 21:389–405

Dundar Y, Dodd S, Strobl J et al (2004) Comparative efficacy of newer hypnotic drugs for the short-term management of insomnia: a systematic review and meta-analysis. Hum Psychopharmacol 19:305–322

Erman MK (2005) Therapeutic options in the treatment of insomnia. J Clin Psychiatry 66(Suppl 9):18–23

Flaherty JH (2008) Insomnia among hospitalized older persons. Clin Geriatr Med 24:51–67

Foley DJ, Monjan A, Simonsick EM et al (1999) Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6,800 persons over three years. Sleep 22(Suppl 2):S366–S372

Glass J, Kl L, Herrmann N et al (2005) Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 331:1169

Hair PI, McCormack PL, Curran MP (2008) Eszopiclone. A review of its use in the treatment of insomnia. Drugs 68:1415–1434

Kripke DF (2007) Greater incidence of depression with hypnotic use than with placebo. BMC Psychiatry 7:42

Kupfer DJ, Reynolds CF 3rd (1997) Management of insomnia. N Engl J Med 336:341–346

Melton ST, Wood JM, Kirkwood CK (2005) Eszopiclone for insomnia. Ann Pharmacother 39:1659–1666

Svarstad BL, Mount JK (2001) Chronic benzodiazepine use in nursing homes: effects of federal guidelines, resident mix, and nurse staffing. J Am Geriatr Soc 49:1673–1678

Vaz Fragoso CA, Gill TM (2007) Sleep complaints in community-living older persons: a multifactorial geriatric syndrome. J Am Geriatr Soc 55:1853–1866

Wolkove N, Elkholy O, Baltzan M et al (2007) Sleep and aging: 1. Sleep disorders commonly found in older people. CMAJ 176:1299–1304